8.0 DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

Although gaps in knowledge remain, a review of the literature addressing the health-related effects of asbestos (and related materials) provides a generally consistent picture of the relationship between asbestos exposure and the induction of disease (lung cancer and mesothelioma). Therefore, the general characteristics of asbestos exposure that drive the induction of cancer can be inferred from the existing studies and can be applied to define appropriate procedures for evaluating asbestos-related risk. Moreover, such procedures provide substantial improvement in the confidence that can be placed in predicting risks in exposure environments of interest compared to predictions derived based on procedures in current use.

Following a general discussions of the findings of this study, specific recommendations (including options) for finalizing a protocol for assessing asbestos-related risks using the procedures identified in this document are provided in Section 8.2. Recommendations are described in Section 8.3 for limited, focused, additional studies to:

(1) settle a small number of outstanding issues (concerning whether the current dose-response models adequately track the time-dependence of lung cancer and mesothelioma) and

(2) provide the data required to fully optimize the approach recommended in this document.

8.1 DISCUSSION AND CONCLUSIONS

8.2.1 Addressing Issues

The issues identified in the introduction (Chapter 2) as part of the focus of this study can now be addressed. These are:

- whether the dose-response models currently in use by the EPA for describing the incidence of asbestos-related diseases adequately reflect the time-dependence for the development of these diseases;

- whether the relative in-vivo durability of different asbestos mineral types affect their relative potency;

- whether the set of minerals included in the current definition of asbestos adequately covers the range of minerals that potentially contribute to asbestos-related diseases;

- whether the analytical techniques and methods currently used for determining asbestos concentrations adequately capture the biologically relevant characteristics of asbestos (particularly with regard to the sizes of the structures included in the various analyses) so that they can be used to support risk assessment; and

- whether reasonable confidence can be placed in the cross-study extrapolation of dose-response relationships that are required to assess asbestos-related risks in new environments of interest.

Time dependence

Regarding the first of the above-listed issues, the lung cancer model appears to adequately reflect long-term risk associated with exposure to amphiboles (for which relative risk remains constant beyond 10 yrs after the end of exposure) but may over-predict long-term risk for chrysotile (Section 6.2.1). Relative risk for chrysotile-exposed individuals appears to decrease substantially with time following 10 yrs after the end of exposure, rather than remain constant, as the model predicts. However, these findings are based on evaluation of only a single chrysotile cohort and a single amphibole cohort so that further evaluation of a minimum of two additional cohorts (one each of amphibole and chrysotile), to determine whether these trends are general, may be warranted (Section 8.3).

Although there are hints from our evaluation that the mesothelioma model may somewhat under-predict long term mesothelioma risk following exposure to amphiboles (Section 6.3.1), the effect appears small and may not be important. Still, because this finding is based on evaluation of only a single amphibole study, evaluation of at least one additional cohort may prove prudent. There was no indication that the mesothelioma model under-predicts risk for chrysotile-exposed individuals, although only small numbers of mesotheliomas were observed in the data sets evaluated for chrysotile.

Biodurability

Because the in-vitro dissolution rate for chrysotile in biological fluids is substantially less than for crocidolite and, likely, other amphiboles (Section 7.2.4), effects potentially attributable to differences in the relative biodurabiliy of these asbestos types are addressed in several sections of this document. Among other things, this difference may explain the reduction in relative risk for lung cancer following cessation of exposure observed for chrysotile-exposed workers that was not apparent for amphibole-exposed workers (Section 6.2.1). Both of these affects may also explain the small difference in potency toward the induction of lung cancer between chrysotile and the amphiboles observed in this study (Section 6.2.4). Importantly, however, the observed difference is

based only on best estimates of relative potency; formally, the difference was not found to be significant.

Although the relative biodurability of chrysotile and the amphiboles may potentially underlie the substantial difference in potency observed between these fiber types toward the induction of human mesothelioma, which is significant, (Sections 6.2.4.2 and 6.3.3.2), direct evidence for the specific effects contributing to this difference are not apparent. Thus, for example, the current mesothelioma model appears to adequately describe the time-dependence for mesothelioma following exposure to both chrysotile and amphiboles (Section 6.3.1), although the chrysotile data sets examined were fairly small, which limits the power of this analysis. Moreover, there is evidence suggesting that, even among the chrysotile-exposed cohorts, the observed mesotheliomas may be attributable to the small concentration of tremolite (amphibole) asbestos that was found as a contaminant in the material to which these cohorts were exposed (Section 6.3.3).

That tremolite fibers represent a substantial (sometimes predominant) fraction of the fibers found in the lungs of deceased workers from these cohorts (Sections 6.2.3 and 7.2.3), despite its trace-level presence in the material handled, suggests either that chrysotile is not deposited as efficiently in the deep lung (which would not be affected by biodurability) or that it is cleared much more rapidly (which may imply a role for biodurability, although size effects may also dominate). Animal retention studies addressing these effects are somewhat ambiguous (Section 7.2.1 and 7.2.2), although they too support the general impression that chrysotile (on a mass basis) is either not deposited as efficiently in the deep lung or cleared more readily from the deep lung (or both). Still, the fact that long fibers of chrysotile (which are expected to contribute most to potency) are observed to be retained for extended periods of time, clouds the potential role for biodurability.

Overall, the substantially larger potency toward the induction of mesothelioma observed in humans may have several causes, but direct evidence for such causes is not definitive either among the supporting animals studies or the in-vitro studies. Thus, while this effect can be adequately addressed by the procedures recommended in this document for risk assessment (because the recommended risk coefficients are based on human data), it cannot be entirely explained.

<u>Minerals of concern</u>

Regarding the range of fibrous minerals that potentially contribute to lung cancer and mesothelioma, available evidence (Sections 7.2 and 7.4) suggests that:

- several minerals and the most biodurable among synthetic fibers (such as erionite or refractory ceramic fibers) in addition to those included strictly within the definition for asbestos have been shown capable of inducing lung cancer and/or mesothelioma (as long as the corresponding fibers fall within the appropriate size range);

- fibrous minerals that differ radically in chemical composition or crystal structure (such as erionite, chrysotile, and the amphibole asbestos types) appear to exhibit substantially different potencies (even after adjusting for size), which may be largely, but not necessarily entirely, explained by relative biodurability; and

- fibrous minerals that exhibit closely related chemical compositions and crystal structures (such as the family of amphibole asbestos types) appear to exhibit relatively similar potencies (once effects are adjusted for size).

Note, to illustrate that biodurability may not entirely describe relative potencies across the different fiber types, the biodurability-based model by Eastes and Hadley (1995 and 1996), which is described in Section 7.2.4, would (properly) predict different potencies for chrysotile and amphiboles for both lung cancer and mesothelioma. However, because the dose-response models for both lung cancer and mesothelioma are linear in fiber concentration, the Eastes and Hadley model would incorrectly predict that the ratio of relative potencies of chrysotile and the amphiboles would be the same in humans for these two diseases, which is definitely not what is observed (Section 6.4).

Given the above-described observations, it is clear that fibrous minerals beyond those included in the definition for asbestos can contribute to lung cancer and mesothelioma. It is also likely that potencies for minerals that exhibit similar chemistry and crystal structure (and which therefore likely exhibit similar physical-chemical properties) also exhibit corresponding potency (for similarly sized fibers). However, the carcinogenicity of fibers exhibiting radically different chemical compositions and crystal structures than those already identified as carcinogenic, should likely be evaluated on a case-by-case basis. Two additional considerations may be useful for focusing such evaluations. First, the size distribution for fibers composed of the mineral of concern should be shown to include substantial numbers within the range of structures that potentially contribute to biological activity (i.e. that fall within the size range defined by the interim index, Equation 7.13). Second, such fibers should also be shown to be relatively biodurable (i.e. that they exhibit dissolution rates less than approximately 100 ng/cm^2-hr, Lippmann 2000). Note that, as long as the interim index of exposure is used to

define fiber sizes, whether a fiber is strictly asbestiform appears to be irrelevant (Appendix B)

Analytical methods

Given the need to detect the thinnest fibers and the need for reliable measurements in outdoor settings, the only analytical technique that appears to be capable of providing quantitative data useful for supporting risk assessment is TEM (Sections 4.3 and 7.5). Further, given the specific size range of structures that need to be evaluated and the specific manner in which they need to be counted (to assure both cross-study comparability and compatibility with the recommended dose-response coefficients), analyses should be performed using the specific analytical methods recommended in this document. These are ISO 10312 (modified to focus on interim index structures) for air and the Modified Elutriator method (Berman and Kolk 2000) for soils or bulk materials. Note that, on a study-specific basis, other methods may be shown to provide comparable results so that they can also be used as part of a properly integrated investigation.

Confidence in risk assessment

Given the degree of reconciliation achieved across the various epidemiology studies (with the adjustments proposed in this document, Section 6.4), it appears that asbestos-related risks estimated using the recommended procedures may be considered good to within one to two orders of magnitude. Further, if proper procedures are employed to derive exposure estimates that are then properly matched with the recommended dose-response coefficients, the chance of severely underestimating risk can be minimized without the need to introduce overly conservative assumptions.

8.1.2 Comparison with Other, Recent Risk Reviews

Although several other reviews have also recently been published that nominally address risk-related issues for asbestos (including questions concerning the identification of an appropriate exposure index and the relative potency of varying fiber types), these studies are either qualitative or involve analysis of data in a manner that does not allow formal evaluation of nature of the specific dose-response relationships for the various diseases. Therefore, they are not well suited to support development of a protocol for conducting formal assessment of asbestos-related risks. Nevertheless, the general conclusions from these reviews are not inconsistent with our findings.

Hodgson and Darnton (2000)

Hodgson and Darnton (2000) conducted a comprehensive quantitative review of potency of asbestos for causing lung cancer and mesothelioma in relation to fiber type. They concluded that amosite and crocidolite were, respectively, on the order of 100 and 500 times more potent for causing mesothelioma than chrysotile. They regarded the evidence for lung cancer to be less clear cut, but concluded nevertheless that amphiboles (amosite and crocidolite) were between 10 and 50 times more potent for causing lung cancer than chrysotile. In reaching this latter conclusion they discounted the high estimate of chrysotile potency obtained from the South Carolina cohort. Hodgson and Darnton concluded that inter-study comparisons for amphibole fibers suggested non-linear dose response relationships for lung cancer and mesothelioma, although a linear relationship was possible for pleural mesothelioma and lung tumors, but not for peritoneal mesothelioma.

The Hodgson and Darnton study was based on 17 cohorts, 14 of which were among the 20 included in the present evaluation. This study had different goals from the present evaluation and used different methods of analysis. Hodgson and Darnton did not use the dose response information within a study. Instead, lung cancer potency was expressed as a cohort-wide excess mortality divided by the cohort mean exposure. Likewise, mesothelioma potency was expressed as the number of mesothelioma deaths divided by the expected total number of deaths, normalized to an age of first exposure of 30, and by the mean exposure for the cohort. These measures have the advantage of being generally calculatable from the summarized data available from a study. However, since they are not model-based, it is not clear how they could be used to assess lifetime risk from a specified exposure pattern, which is an important goal of the current project. Use of average cohort exposure could cause biases in the estimates, if, e.g., a large number of subjects were minimally exposed. Also, the recognized differences between studies in factors, in addition to level of exposure, that may affect risk will also affect the reliability of conclusions concerning the dose response shape based on comparisons of results across studies.

Lippmann (1994 and 2000?)

In the most recent of these reviews, although based on a qualitative, anecdotal treatment of the literature, Lippmann reinforces our general findings that it is longer fibers (those longer than a minimum of approximately 5 µm) that contribute to lung cancer and mesothelioma. He further indicates that, based primarily on the limits observed for fibers that can be phagocytized, fibers that contribute most to lung cancer are likely longer than a minimum of 10 µm. In his review, based on a series of comparisons of mean and median dimensions reported for the relevant exposures across a broad range of studies, Lippmann draws several fairly specific conclusions on the ranges of fiber sizes that may contribute to various diseases (i.e. that the minimum length fibers that contribute to asbestosis, lung cancer, and mesothelioma are 2, 5, and 10 µm, respectively). He also suggests that fibers that contribute to mesothelioma may

need to be thinner than 0.1 µm while those that contribute to lung cancer may need to be thicker than 0.15 µm. While it is not clear that drawing such specific conclusions can be firmly supported by the kinds of qualitative comparisons across reported mean and median dimensions for exposures in various studies that are described in this paper, the author indicates that further, more formal study of the dose-response relationships that he posits is warranted. It is noted that many of the studies reviewed by Lippmann are the same studies also incorporated in our analysis.

In the earlier review, Lippmann plots lung tumor incidence as a function of inhaled animal dose for data from a series of broadly varying studies based, respectively, on fibers longer than 5, 10, and 20 µm (no widths considered) and suggests that the quality of the fits are comparable. The author further suggests, based on this evaluation, that PCM seems to provide a reasonable index of exposure. However, no formal goodness of fit tests were performed in this analysis and, based on visual inspection, none of the plots would likely show an adequate fit. Moreover, the plot of the tumor response vs. dose as a function of fibers longer than 5 µm appears to be substantially worse than the other two plots; if one removes the single highest point in this plot, it appears that any sign of correlation will largely disappear.

Stayner et al. 1996

In the context of evaluating the "amphibole hypothesis", Stayner *et al.* computed the excess relative risk of lung cancer per fiber/ml/yr from 10 studies categorized by the fiber types to which the cohort was exposed. Each of these studies was also included in the present evaluation. Both the lowest and highest excess relative risks came from cohorts exposed exclusively to chrysotile. Based on their evaluation, they concluded that the epidemiologic evidence did not support the hypothesis that chrysotile asbestos is less potent than amphibole for inducing lung cancer. However, based on a review of the percentage of deaths in various cohorts from mesothelioma, they concluded that amphiboles were likely to be more potent than chrysotile in the induction of mesothelioma. They also noted that comparison of the potency of different forms of asbestos are severely limited by uncontrolled differences in fiber sizes. None of these conclusions are inconsistent with our general findings.

8.2 RECOMMENDATIONS FOR ASSESSING ASBESTOS-RELATED RISKS

Recommended risk coefficients for lung cancer and mesothelioma (the adjusted K_L values and K_M values) are provided in Tables 6-29 and 6-30, which present best-estimate recommendations and conservative recommendations, respectively. Once it is decided which of these sets of risk coefficients to adopt for general use, the selected set can be incorporated into the procedures described below to evaluate asbestos-related risk. Consistent with the evidence presented elsewhere in this report of a

different potency for chrysotile and amphibole (Chapter 6), separate risk coefficients are recommended for chrysotile and the amphiboles.

Importantly, the risk coefficients provided in Tables 6-29 and 6-30 are adjusted to be specifically combined with exposure estimates expressed in terms of the interim exposure index defined by Equation 7-13. Such exposure estimates include *only* asbestos structures longer than 5 µm and thinner than 0.5 µm with those longer than 10 µm weighted more heavily (as described in the equation). Combining the risk coefficients with measurements expressed in terms of any other index of exposure (such as the PCME index in current use) will result in invalid estimates of risk. Note, as indicated in Appendix B, all structures satisfying the dimensional criteria for this index (and exhibiting the requisite mineralogy) should be included in analyses for determining asbestos concentrations; it is not necessary (for example) to distinguish between true asbestiform fibers and cleavage fragments when the interim index is employed.

Three options are described below for evaluating asbestos-related lung cancer and mesothelioma risks using the risk coefficients defined in Tables 6-29 or 6-30 with appropriately derived exposure estimates (expressed in terms of the interim exposure index defined by Equation 7-13). Additional considerations for determining asbestos exposure concentrations are also provided.

Option 1: Using the EPA Dose-Response Models

If there is interest in estimating risk for a particular population that involves time-varying exposures (or a cohort that potentially experiences background mortality rates substantially different from the general population), the EPA models for lung cancer (Equation 6.2) and for mesothelioma (Equation 6.11, for constant exposure, or Equation 6.12 for time-varying exposure) may be directly used to assess risk. This requires knowledge of both the age-specific background lung cancer mortality rate for the population of interest and the age-specific total mortality rate for this population, in addition to the data describing the overall pattern of exposure. The mortality rates can then be used in a lifetable analysis, along with the given exposure pattern and the appropriate values of K_{L^*} and K_{M^*} (either from Table 6-29 or 6-30) to estimate the additional probability of dying of lung cancer or mesothelioma. Such a lifetable analysis is described in Appendix D.

Option 2: Estimating Risk from a Risk Table

Once it is decided which of the two sets of recommended risk coefficients (Table 6-29 or 6-30) to adopt for general use, a risk table can be constructed (using general U.S.

mortality rates) that can then be applied broadly to assess risk. To illustrate this approach, Table 8-1 is a risk table (for lifetime, continuous exposure) that was constructed using the risk coefficients from Table 6-30 (i.e. the "conservative" values).

Note that the values in the table have already been adjusted for lifetime, continuous exposure (so conversions from an occupational exposure scenario are not required).

The only data required to assess risks using this risk table are estimates of long-term average exposure (*derived from appropriate measurements, as described below)* for each particular exposure scenario and population of interest.

Table 8-1 presents estimates of the additional risk of death from lung cancer and mesothelioma attributable to lifetime exposure at an asbestos concentration of 0.0005 f/ml (for fibrous structures longer than 5 µm and thinner than 0.5 µm) as determined using TEM methods recommended below. In the table, separate risk estimates are provided for males and females and for smokers and non-smokers. Separate estimates are also presented for exposures containing varying fractions (in percent) of fibrous structures longer than 10 µm.

Separate estimates are presented for smokers and nonsmokers because the lifetime asbestos-induced risk of both lung cancer and mesothelioma differ between smokers and non-smokers. The asbestos-induced risk of lung cancer is higher among smokers because the lung cancer model (Equation 6.2) assumes that the increased mortality rate from lung cancer risk due to asbestos exposure is proportional to background lung cancer mortality, which is higher among smokers. This is consistent with the muitplicative effect between smoking and asbestos exposure reported by several researchers (see, for example, Hammond et al. 1979).

The asbestos-induced risk of mesothelioma is smaller among smokers because the mesothelioma model (Equation 6.11) assumes that risk from constant exposure increases with the cube of age, with the result that the predicted mortality rate is highest among the elderly. Thus, since smokers have a shorter life span than non-smokers, their risk of dying from mesothelioma is also predicted to be smaller.

Table 8-1

Separate estimates are provided for different fractions of fibrous structures longer than 10 µm because the model assumes that structures longer than 10 µm are more potent than structures between 5 and 10 µm in length (in a manner consistent with Equation 7.13). The derivation of this model is described in detail in Chapters 6 and 7. Risks from lifetime exposures to asbestos levels other than 0.0005 may be estimated from the appropriate entry in Table 8-1 by multiplying the value in the selected cell from the Table by the airborne asbestos concentration of interest and dividing by 0.0005 (i.e., by assuming that the additional risk is proportional to the asbestos exposure level). Airborne asbestos concentrations to be used in this manner *must* be estimates of lifetime average exposure and *must* be expressed as structures longer than 5 µm and thinner than 0.5 µm derived as described below. Estimates of the fraction of these structures that are also longer than 10 µm must also be determined to select the appropriate cell of the table from which to derive the risk estimate. Note that the two size fractions that are combined to determine C_{asb} (Equation 7.13) are separately enumerated (not combined) when they are to be used in conjunction with Table 8-1.

The procedure described above for estimating risks using Table 8-1 should provide good approximations as long as the projected risk is no greater than 1,000 per 100,000. Risks greater than 1,000 per 100,000 (i.e. 1 in 100) that are derived from the Table are likely to be over-estimated. However, for risks associated with short-duration exposures or exposures that differ radically over time, it may be better to use a lifetable analysis or a modified version of Table 8-1. This is to avoid substantially under- or over-estimating risk (depending on how the table might otherwise be applied).

Table 8-1 was derived using the approach described in Appendix D by incorporating the age-, sex-, and smoking-specific death rates reported for the general U.S. population and assuming that exposure is constant and continuous at the level indicated in the table. The underlying models are provided in Chapter 6 for cases in which exposure is either not constant or not continuous and for which sufficient data exist to characterize the time-dependence of such exposure. If available, there may also be cases in which it is advantageous to employ mortality data from a control population that better matches the exposed population of interest than the U.S. population as a whole.

Option 3: Estimating Risk from a Unit Risk Factor

A third option for estimating risks based on the approach recommended in this document would be to derive a combined, unit risk factor for asbestos cancer risk similar to the unit risk factor currently recommended by EPA. The new unit risk factor would be derived using the selected set of new risk coefficients (either those in Table 6-29 or Table 6-30) and would be appropriate for use with exposure estimates expressed in terms of the interim exposure index (rather than the PCME index, as currently recommended). As with the unit risk factor currently in use, some estimate of the fraction of smokers in the general population would also need to be provided as an

input. This approach, however, may prove to be somewhat less flexible than the second option above and therefore may be prone to greater errors.

Requirements for Asbestos Measurements

One additional advantage of the approach for evaluating asbestos-related risks recommended in this document (in comparison to the current approach) is that the procedure for assessing risks is tied unambiguously to a specific index for measuring and expressing exposure (i.e. the interim index) and this, in turn, is tied unambiguously to requirements for analyzing asbestos samples.

Estimates of airborne asbestos concentrations that are required to support risk assessment can be derived either by extrapolation from airborne measurements or by modeling release and dispersion of asbestos from sources (soils or other bulk materials). In either case, exposure estimates must be representative of actual (time-dependent or time-integrated) exposure and must provide measurements of the specific size fractions of asbestos that are components of the interim exposure index defined by Equation 7.13. Additional considerations that need to be addressed to assure the validity of risk estimates derived using this protocol include:

- the array of samples collected for estimating airborne asbestos concentrations must be representative of the exposure environment;
- the time variation of airborne asbestos concentrations must be properly addressed;
- airborne samples must to be collected on membrane filters that are suitable for preparation for analysis by transmission electron microscopy (TEM). Appropriate procedures for sample collection are described in Chatfield and Berman (1990) or the ISO Method (ISO 10312)[1];
- sample filters must be prepared for analysis using a direct transfer procedure (e.g. ISO 10312). Should indirect preparation be required (due, for example, to problems with overloading of sample filters), a sufficient number of paired samples will need to be collected and analyzed to

[1] Note that the ISO Method (ISO 10312) is a refinement of the method originally published as the Interim Superfund Method (Chatfield and Berman 1990). It incorporates improved rules for evaluating fiber morphology. Both methods derive from a common development effort headed by Eric Chatfield.

establish a site-specific correlation between directly and indirectly prepared samples;

- samples must be analyzed by TEM;

- samples must be analyzed using the counting and characterization rules defined in ISO 10312 with one modification: only structures longer than 5 µm and thinner than 0.5 µm need to be enumerated. Separate scans for counts of total structures longer than 5 µm and longer than 10 µm are recommended to increase the precision with which the longest structures are enumerated. Importantly, ISO Method rules require separate enumeration and characterization of component fibers and bundles that are observed within more complex clusters and matrices. Such components, if they meet the dimensional criteria defined in Equation 7.13 must be included in the structure count;

- if risks are to be estimated using the risk models (as described in the first option), asbestos concentrations derived from the above-described measurements must be expressed as the weighted sum of structures between 5 and 10 µm in length and structures longer than 10 µm in length, per the exposure index defined in Equation 7.13. Only structures thinner than 0.5 µm are to be included in these counts. Both fibers and bundles that are isolated structures and fibers and bundles that are components of more complex structures are to be included in structure counts (as long as each structure counted satisfies the defined size criteria for the size category in which it is included);

- if risks are to be estimated using the risk models (the first option), the risk coefficient(s) selected either from Table 6-29 or 6-30 must be appropriate for the fiber type (i.e. chrysotile or amphibole) and the disease end point (i.e. lung cancer or mesothelioma) relevant to the situation of interest; and

- if risks are to be estimated using Table 8-1 (The second option), rather than deriving the weighted sum described in Equation 7.13, the concentration of asbestos structures longer than 10 µm and thinner than 0.5 µm must be derived to determine the appropriate column of the Table from which to estimate risk and the concentration of total asbestos structures longer than 5 µm and thinner than 0.5 µm must be derived, divided by 0.0005, and multiplied by the risk estimate listed in the appropriate cell of the Table to generate the risk estimate of interest.

Considerations that need to be addressed to assure the validity of risk estimates derived from soil or bulk measurements combined with release and transport modeling include:

- the array of samples collected for estimating source concentrations must be representative of the surface area or volume of source material from which asbestos is expected to be released and contribute to exposure;

- samples must to be prepared and analyzed using the Modified Elutriator Method for soils and bulk materials (Berman and Kolk 1997, 2000), which is the only method capable of providing bulk measurements that can be related to risk;

- membrane filters samples prepared using the tumbler and vertical elutriator per the Superfund method must themselves be prepared for TEM analysis using a direct transfer procedure;

- TEM analysis must be conducted using the counting and characterization rules defined in the ISO Method (ISO 10312) in precisely the same manner that is described above for air measurements. Also, the same size categories need to be evaluated in the same manner described above, whether results are to be used to support assessment using risk models or using the risk table; and

- release and dispersion models that are selected for assessing risks must be appropriate to the exposure scenario and environmental conditions of interest. Such models must also be adapted properly so that they accept input estimates expressed in terms of fiber number concentrations. Procedures suggested for adapting such models are illustrated in a recent publication (Berman 2000).

Note, if we design analytical procedures to focus on long structures, we can evaluate risks cost-effectively. Moreover, even to the extent that shorter structures or other structures might contribute to risk should generally be addressed by default. The alternate approach of spending most time and money counting lots of (potentially non-potent or marginally potent) short structures while not characterizing longer structures with adequate sensitivity or precision (which is embodied in the current EPA approach) leaves the much greater and more probable danger of falsely missing potentially serious hazards because a small population of extremely potent, long fibers were missed in a particular environment.

8.3 RECOMMENDATIONS FOR FURTHER STUDY

A small number of limited and focused studies (described previously) are previously recommended in this document because they are likely to provide very cost-effective improvements to the quality of this document and may support substantial improvement to the recommended procedures for assessing asbestos-related risks. The recommended studies are:

(1) a focused study to expand our evaluation of the ability of the current EPA models to adequately track the time-dependence of disease (Sections 6.2.2 and 6.3.2); and

(2) a focused study to develop the supporting data needed to define adjustments for potency factors that will allow them to be used with an exposure index that even more closely captures asbestos characteristics that determine biological activity than the currently proposed "interim index" (Section 7.5).

Note that, by properly designing the second of the above-listed studies, it may also be possible to further address another outstanding issue that was previously identified: the question of whether dose-response coefficients derived from mining studies are under-estimated relative to studies involving asbestos products because exposures in the mining studies may contain large numbers of non-asbestos particles contributed by the disturbance of host rock (Section 6.2.3).

For the first of the above-recommended studies, we would need to acquire the raw data from at least one additional cohort exposed primarily to chrysotile and one additoinal cohort exposed primarily to amphiboles to determine whether our observation that the current EPA model for lung cancer adequately describes the time dependence of relative risk associated with exposure to amphiboles but not to chrysotile. Should this finding be confirmed, the potential magnitude and importance of the deviation would also be evaluated along with a candidate adjustment to the model that would likely solve the problem. Simultaneous, additional analysis of the mesothelioma model may also be useful.

Candidate cohorts that may be useful for this evaluation, if they can be acquired, include: (for amphibole exposures) the lung cancer data and *newest* mesothelioma data from Libby (best) or, potentially the lung cancer and mesothelioma data from the Paterson, New Jersey insulation manufacturing plant studied by Seidman and (for chrysotile exposures) the lung cancer data from Quebec (best) or, potentially, the lung cancer and mesothelioma data from the New Orleans asbestos-cement pipe plant studied by Hughes et al. The possibility of obtaining some or all of these data sets needs to be further explored.

For the second of the above-listed studies, we would need to obtain suitable bulk samples of raw ore from the Wittenoom, Libby, and Quebec mines and bulk samples of textile grade (and several other grade) products from the Quebec mines. We have already approached individuals who can provide access to these materials and they have all expressed interest in collaborating.

Ideally, a well-designed field sampling plan would be used to collect and composite raw ore samples and multiple samples (from widely dispersed time-periods of production) would be collected and composited for the fiber product samples. The resulting, limited number of well-constructed composite samples would then be prepared using the Modified Elutriator Method (Berman and Kolk 2000) and subjected to a rigorous analysis by TEM (covering counting and characterization of a very broad range of fibrous structures and non-fibrous particles). The data from these analyses would then be used both to evaluate questions concerning the quality of exposure at mining sites and to adjust the dose-response coefficients derived from studies of these mining sites (and several other studies of facilities that used the products from Quebec). The coefficients would be adjusted to a better optimized exposure index (in which fibers at least as long as 20 µm would be separately weighted) and the degree to which use of this new index improves agreement across certain selected studies would be evaluated.